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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,873	09/30/2003	John Chan	COTH-P01-002	7993

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ROPES & GRAY LLP
PATENT DOCKETING Floor 39
One International Place
Boston, MA 02110-2624

EXAMINER	
DEJONG, ERIC S	
ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,873	CHAN ET AL.	
	Examiner	Art Unit	
	ERIC S. DEJONG	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007 and 26 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-13,15,16,21-24,27-33,35 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-13,15,16,21-24,27-33,35 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/24/2007 has been entered.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 2, 6, 14, 17-20, 25, 26, 34, 36-55, and 57-68 are cancelled. Claims 1, 3-5, 7-13, 15, 16, 21-24, 27-33, 35, and 56 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7-13, 15, 16, 21-24, 27-33, 35, and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must be able to modify a recipient polypeptide that binds a target by replacing an identified set of amino acid residues within said polypeptide with an identified spatially conserved protease motif, such that the engineered polypeptide would retain both of said binding and

protease activities. For reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The disclosure provides methods and procedures for carrying out *in silico* modeling of a recipient polypeptide to contain a spatially conserved protease motif. The instant disclosure further provides guidance for testing for proteolytic activity in a polypeptide. However, the disclosure does not provide detailed guidance on how to computationally model a polypeptide to contain a protease motif such that the modeled polypeptide, when synthesized, will retain the predicted protease activity.

c) The disclosure provides examples of computationally identifying proteolytic sites that are suitable for engineering into a similar geometric region of a recipient polypeptide. The instant disclosure further provides guidance for testing for proteolytic activity in a polypeptide. However, the instant disclosure does not provide working examples wherein a computationally modeled polypeptide containing a protease motif was further synthesized and demonstrated to maintain a predicted protease activity.

d) The nature of the invention, modeling and engineering polypeptides to introduce a an active protease domain, is extremely complex.

e) The prior art shows that prediction of structure and activity in polypeptides can be reliably accomplished only if very close homologs of known structures are available and if said homologs further share high degrees of structural, sequence and activity similarity. A recent review of protein modeling and structure prediction provided by Ginalski et al. published on states:

"Theoretically, it should be possible to deduce structure from sequence by accurate simulation of physical processes. We are very far from achieving this goal, and the methods of practical importance

were traditionally based on the observation that proteins with similar sequences are structurally similar as well." (Ginalski et al., page 1874, column 1, line 15 through column 2, line 5)

and

"Predicted protein structures can be used if very close homologs with known structure are available… Currently available structure prediction methods do not allow for high-quality predictions of the quaternary structure of protein complexes and for the prediction of interactions between proteins. Current benchmarks indicate that methods predicting interactions can be successful mainly in cases when structures exhibit minimal conformation changes upon complex formation. Substantial errors observed in predicted models go beyond the limits tolerated by such methods." (Ginalski et al., page 1887 column 1, line 45 through column 2, line 2).

The instantly claimed method only requires that a recipient polypeptide have a set of amino acid residues that match a spatially conserved motif derived from a separate set of amino acids residues from a protease motif. The instant claims do not set forth a requisite level of matching such that the overall structure of recipient polypeptide, following the substitution of the amino acids derived from a protease domain, will exhibit only minimal conformational changes. Further, the instantly claimed method does not require any sequence similarity between an original set of amino acids native to a recipient polypeptide and the set of amino acids derived from a protease motif that is to be substituted into said recipient polypeptide. Further, the instantly claimed method does not require any similarity in the activity between the original set of amino acids native to a recipient polypeptide and the set of amino acids derived from a protease motif that is to be substituted into said recipient polypeptide .

f) The skill of those in the art of polypeptide modeling and structure prediction is extremely high.

g) The predictability of successfully engineering a polypeptide to contain an active protease domain is unknown in the art. Successful applications of predicting protein structure and activity have been identified in the art for cases where very close

homologs were available that further maintained high sequence, structure, and activity similarity.

h) The claims are broad in that they encompass engineering spatially conserved protease motif into a generic recipient polypeptide.

The skilled practitioner would first turn to the instant disclosure for guidance in using the claimed invention. However, the disclosure does not provide detailed guidance on how to model polypeptides containing a protease motif such that the modeled polypeptides, when synthesized, will predictably retain any predicted protease activity. As such, the skilled practitioner would turn to the prior art for such guidance, however the predictability of successfully engineering a polypeptide to contain an active protease domain is unknown in the art. Finally, said practitioner would turn to trial and error experimentation to determine which, if any, engineered polypeptides actually have an active protease domain. Such amounts to undue experimentation.

Response to Arguments

Applicant's arguments filed 03/26/2008 have been fully considered but they are not persuasive.

In regard to the rejection of claims under 35 USC § 112, first paragraph, applicants argue that the instant claims as amended are directed to screening or testing methods to assess the possibility of incorporating a functional protease motif into a recipient polypeptide to confer protease activity. Applicants further argue that this is

loosely analogous to a drug screening method wherein the methods are always enabled regardless of whether a "yes" or "no" answer is reached.

In response to applicant's arguments, it is first noted that applicants argument is directed the recitation of an intended use set forth in the preamble of the instant claims. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). It is further noted that applicants analogy fails to account for the explicit process steps (see steps a)-c) of instant claim 1) directed towards generating a modified recipient polypeptide. As such, the instant claim is not directed to a drug screening method, as argued by applicants, but rather a process of generating recombinant proteins with new protease activity. Therefore, it is maintained that the instant claims fail to satisfy the enablement requirement under 35 USC 112, first paragraph, because a practitioner would turn to trial and error experimentation to determine which, if any, engineered polypeptides actually have an active protease domain.

Applicants further argue that even if what the examiner was arguing is correct, that one of ordinary skill in the art would always be able to carry out the claimed

methods to determine whether or not a protease motif can be engineered into the recipient [polypeptide].

In response, it is acknowledged that one of ordinary skill in the art can carry out expression and testing procedures to determine if a given polypeptide has protease activity (see also item c) in the instant rejection set forth above). However, applicants argument is essentially that one of ordinary skill in the art can resort to trial and error experimentation in order to practice the claimed invention (i.e. express and test for protease activity with any and all modified recipient proteins generated by the instant claims). As set forth in the instant rejection, the instant disclosure does not provide convincing evidence that any functionally modified recipient polypeptide with a protease activity can be reliably or predictably generated by the claimed process without resorting to undue experimentation.

Applicants arguments further fail to address the absence of working examples in the instant specification and the teachings of the prior art that for the basis of the instant rejection. It is reiterated that the instant claims considers only the spatial arrangement of amino acid residues in the recipient protein. The instant claims do not further address or consider how the alteration of the recipient polypeptide sequence to contain new amino acids residues (corresponding to said protease domain) will effect overall structure and activity of the real-world polypeptide. Ginalski et al. does address modeling techniques wherein a polypeptide sequence is modeled to match an existing or known structure (see Ginalski et al., page 1879, col. 1, line 33 through page 1880, col. 1, line 44).

Regarding modeling and prediction approaches that fits a given sequence to a predicted structure, Ginalski et al. explicitly teaches:

"In the first approach... the surrounding structural environments for each residue of the query are kept identical to those observed in the template structure. This procedure is as fast as aligning a profile with a sequence but has important disadvantage that calculated in such a way local environments have little in common with those that might be observed in the native structure of the query protein. Most of them are essentially wrong, as majority of surrounding residues in template structure are replaced by different amino acids in the query protein."

This teaching from Ginalski et al. provides direct support that one of skill in the art would not be able to reliably predict what structure or activity, if any, a real-world engineered polypeptide sequence will actually possess, since the instant method of engineering relies only on modeling the spatial arrangement of amino acids between said protease domain and a set of native amino acids from the recipient polypeptide sequence. Therefore, it is maintained that a skilled practitioner would have to resort to trial and error experimentation in order to successfully engineer a recipient polypeptide so as to contain an active protease motif as instantly claimed. Such amounts to undue experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. DEJONG whose telephone number is (571)272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Moran Marjorie can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S DeJong/
Primary Examiner, Art Unit 1631